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2025 AAPS 360 Annual Meeting: Highlights in In Vitro Release and Dissolution Testing and Oral Biopharmaceutics Modeling

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ABSTRACT

This manuscript highlights key sessions from the In Vitro Release and Dissolution Testing (IVRDT) and Oral Biopharmaceutics and Absorption Modeling (OBAM) communities at the 2025 AAPS PharmSci 360 Annual Meeting (November 9–12, San Antonio, TX). Presentations emphasized a shift toward mechanistic and predictive in vitro and in silico tools, including enzymatic dissolution media, physics-based particle dissolution modeling, physiologically based biopharmaceutics modeling (PBBM) applications for food-effect assessment and specification setting, advanced gastrointestinal simulation platforms, AI-driven formulation optimization, and the complementary role of preclinical animal studies. Collectively, these sessions underscored the value of integrating biorelevant experimentation with computational modeling to streamline and de-risk oral drug development.

KEYWORDS: In vitro release and dissolution testing (IVRDT), oral biopharmaceutics and absorption modeling (OBAM), biorelevant dissolution, biopredictive, physiologically based biopharmaceutics modeling (PBBM), dissolution modeling

INTRODUCTION

The American Association of Pharmaceutical Scientists (AAPS) successfully hosted its PharmSci 360 Annual Meeting and Exposition from November 9–12, 2025, at the San Antonio Convention Center in San Antonio, TX. As one of the premier global gatherings for pharmaceutical scientists, this event fosters collaboration among experts from academia and industry (Fig. 1).

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#Tahseen Mirza did not attend the AAPS 360 meeting but contributed as the Chairman of the IVRDT Community in organizing, topics selection, and in manuscript review.

This year, the In Vitro Release and Dissolution Testing (IVRDT) and Oral Biopharmaceutics and Absorption Modeling (OBAM) communities played an especially meaningful role by recommending a curated selection of scientific sessions, emerging hot topics, and keynote speakers. These recommendations were thoughtfully developed in direct response to the needs and priorities expressed by their community members, ensuring that the programming addressed the most current, relevant, and pressing scientific challenges. The resulting sessions not only highlighted cutting edge advancements but also reflected the collective interests and values of these vibrant scientific communities. In this highlight manuscript, we provide a concise summary of the presentations, discussions, and scientific advancements featured in these community driven sessions. Our goal is to capture and disseminate the key insights shared by the speakers, with a particular focus on the topics most relevant to the IVRDT and OBAM communities. By doing so, we aim to amplify the knowledge exchanged at PharmSci 360 and support continued learning across our scientific networks.

Industrial and academic presenters discussed topics related to advancing biorelevant dissolution and absorption prediction by integrating in vitro, in silico and mechanistic modeling approaches with preclinical and clinical studies. Speakers highlighted how enzymatic effects, formulation design, and dosage-form–specific behavior (e.g., amorphous solid dispersions and orodispersible tablets) influence dissolution and downstream exposure. A strong theme was the expanding role of PBPK/PBBM to link dissolution to systemic and local gastrointestinal (GI) drug performance, including case studies on food effects, specification setting, and locally acting drugs like mesalamine. Several presentations examined current

Figure 1. Photo captured at the IVRDT dinner during PharmSci 360 (November 2025) along the San Antonio Riverwalk. Left side: Niloufar Salehi, Vivian Gray, Aleksander Mendyk, Ishai Nir, and Sanjaykumar Patel. Right side: Andre Herman, Nikoletta Fotaki, Mark Liddell, Jie Shen, Pradnya Bapat, Alger Salt, and Zhao Liu.
IVRDT: In Vitro Release and Dissolution Testing.

gaps, advances, and future opportunities in mechanistic dissolution modeling and computational analysis. Overall, the talks emphasized a shift toward predictive, mechanistic in vitro and in silico tools to de-risk oral drug development.

This report highlights some of the main hot topics, symposiums, and keynote presentations, including the following:

Rapid Fire Sessions:

- Enhancing biorelevance: unveiling enzymatic impact on simulated GI dissolution
    - *Catarina I. D. Chendo, MS, Hovione*
- In vitro + in silico: advanced tools for absorption prediction
    - *Balint Sinko, PhD, Pion Inc*

Hot Topic Session:

- Identifying gaps and pushing boundaries in mechanistic dissolution modeling
    - *Deanna M. Mudie, PhD, Simulations Plus, Inc*
    - *Yanxing Wang, PhD, New Mexico State University*
    - *Jozef Al-Gousous, PhD, Johannes Gutenberg University Mainz and University of Michigan*

Symposium Sessions:

- Advanced in vitro GI simulation and physiologically-based biopharmaceutics modeling (PBBM) to support oral drug development
    - *Connor O'Farrell, PhD, InnoGI Technologies*
- Advances in computational analysis of dissolution (ASD)
    - *Rob Tzuchi Ju, PhD, Abbvie Inc.*
- Advances in computational analysis of dissolution: orodispersible tablets
    - *Aleksander Mendyk, MSC, PhD, DSC, Jagiellonian University Medical College*
- De-risking formulation strategies using PBBM: mechanistic case studies on evaluating food effects and guiding dissolution specifications
    - *Deanna M. Mudie, PhD, Simulations Plus, Inc.*
- Mechanistic PBPK modelling for the locally acting git drug: mesalamine
    - *David B. Turner, PhD, Certara Predictive Technologies, Certara UK Limited*

Keynote Session:

- Current status and future perspective of pre-clinical in vivo studies vs in vitro/in silico predictive biopharmaceutics tools
    - *David C. Sperry, PhD, Eli Lilly and Company*

RAPID FIRE SESSIONS

Catarina Chendo addressed limitations of conventional biorelevant dissolution methods that excluded digestion by developing an improved simulated GI dissolution approach that integrates enzymatic digestion and food effects to better reflect human physiology. Pepsin and pancreatin were incorporated into fasted and fed simulated gastric and intestinal fluids, and enzymatic activity was confirmed using protein substrates that showed rapid digestion under fasted conditions and slower, pH dependent digestion in fed media. Two case studies with USP apparatus 2 demonstrated the impact on dissolution: a spray dried lysozyme formulation showed rapid release in enzyme free fasted media but substantial loss in enzyme containing media due to proteolysis, highlighting limitations of enzyme free methods for protein based drugs, whereas an itraconazole amorphous solid dispersion with a protein excipient exhibited enhanced intestinal dissolution in the presence of enzymes due to matrix cleavage. Overall, the enzyme integrated method captured both enzymatic degradation and food effects, improving the physiological relevance and translational value of in vitro dissolution data for formulation design and early development decisions.

Dr. Balint Sinko focused on key learnings from the development and evaluation of advanced formulation strategies for poorly soluble BCS Class II and IV compounds, highlighting how dissolution permeation (flux) assays combined with physiologically relevant mechanistic modelling improved understanding of oral absorption. While advanced approaches such as amorphous solid dispersions and nanonization enhanced apparent solubility, the case studies showed that flux data alone were insufficient to predict in vivo performance due to factors such as limited membrane geometry and particle drifting. Integrating modelling with in vitro data enabled identification of rate limiting absorption

steps, clarification of dose dependent shifts between dissolution-limited, permeability-limited, and solubility limited absorption, and reconciliation of apparent in vitro differences with observed in vivo bioequivalence. Overall, the presentation demonstrated that coupling flux assays with mechanistic modelling strengthened in vitro–in vivo translation, reduced formulation selection risk, and supported more confident progression toward clinical evaluation.

HOT TOPIC SESSION

The hot topic moderated by Dr. Deanna Mudie and panelists addressed the gap between empirical dissolution approaches and the need for mechanistic understanding when dissolution interacts with complex physiological processes. Dissolution was shown to be a critical determinant of oral bioavailability for poorly soluble drug products, and although in vitro–in vivo correlation methods linked dissolution to systemic exposure, they often lacked explanatory power. Mechanistic dissolution modeling was highlighted as a way to describe the underlying physical and chemical processes using measurable drug, formulation, and GI properties, enabling identification of key performance attributes, optimization of release profiles, linkage of in vitro and in vivo dissolution, and support for setting dissolution specifications (*1*, *2*). When integrated within physiologically based biopharmaceutic modeling (PBBM) frameworks that capture GI transit, permeation, distribution, metabolism, and excretion, mechanistic dissolution models can support prediction of pharmacokinetics across populations (*3*). Many existing mechanistic and semi-mechanistic models have shown utility in predicting in vitro and in vivo dissolution (*4*, *5*). However, improvements can be made to increase applicability since many are specific to particular in vitro setups and/or conflate multiple effects, such as shear and convection, limiting generalizability. Such approaches can cause difficulties in translating between in vitro and in vivo conditions, particularly for particles larger than 20 µm in radius, and/or large aspect ratios dissolving in nonquiescent environments (*5*, *6*). Furthermore, increased understanding of convection-enhanced diffusion and electrochemical gradients is needed to improve prediction accuracy of weakly basic drug dissolution in unbuffered media representative of the fasted stomach. This hot topic session highlighted recent advances aimed at overcoming these challenges, including improved prediction of ionizable drug dissolution in unbuffered media and physics-based approaches that explicitly account for particle shape, polydispersity, and fluid hydrodynamics in both in vitro and in vivo contexts.

Dr. Yanxing Wang presented a physics-based framework that advances mechanistic dissolution modeling by moving beyond the oversimplified assumption of spherical drug particles in idealized flows. The work demonstrates that non-spherical particle geometry alone even under inertia-free creeping-flow conditions generates complex, quasi-periodic, and chaotic rotational dynamics in triaxial ellipsoidal particles, directly impacting surface renewal and local mass transfer. When weak inertia is introduced, the transient evolution toward stable rotational states produces structured, time-dependent flow fields that significantly alter convective transport near the particle surface. For sharp-edged cuboidal particles, which better represent real pharmaceutical solids, edges and corners act as micro-stirrers inducing localized vortices and flow separation that create enhanced and distinct mass transfer pathways. At the intestinal scale, peristaltic wave models revealed that cooperative interaction between two waves can drive chaotic mixing even at very low Reynolds numbers, with tunable wave parameters controlling the location and intensity of mixing suggesting the body may actively regulate dissolution and absorption through coordinated muscular contractions. Together, this work links particle geometry, weak inertia, and intestinal hydrodynamics into a unified mechanistic framework for more physiologically relevant dissolution prediction. The authors gratefully acknowledge Dr. Niloufar Salehi and Dr. Youlin Liu of Eli Lilly and Company for their valuable insights and constructive discussions. This work was supported by the National Science Foundation ERI Program (award no. 2138740) and CAREER Program (award no. 2443848).

Dr. Jozef Al-Gousous challenged the long-standing stagnant film dissolution models by demonstrating that both the thermodynamic approach and the Mooney et al. model produce large systematic errors in unbuffered reactive media, with three- to four-fold underestimation and two- to three-fold overestimation of experimental fluxes, respectively, for weakly basic drugs (*7*). These errors stem from the fundamental difference between convective diffusion and stagnant film diffusion in their sensitivity to diffusivity discrepancies among reacting species. Numerically solving the comprehensive convection-diffusion-reaction (CDR) equation reduced prediction errors to under 20%, and analytical solutions were further derived for two physiologically relevant limiting cases: high background electrolyte (in vivo gastric) and zero background electrolyte (in vitro regulatory media), offering computational simplicity

without sacrificing accuracy. Key findings revealed that proton diffusion from bulk to interface, not drug diffusion away from it, is the rate-limiting step in weak base gastric dissolution, and that convection actively influences surface pH, contradicting conventional assumptions. For suspended particles, surface pH was shown to depend on both particle size and agitation rate, underscoring the need for accurate fluid dynamic models to predict dissolution of real pharmaceutical particles with complex geometries.

SYMPOSIUM SESSIONS

Dr. Connor O'Farrell demonstrated the integration of the TIM platform of advanced in vitro GI models with PBBM to support oral drug development (*8*). While compendial USP apparatus remain appropriate for quality control, the tiny-TIM and TIM-1 models of the upper GI tract provide greater biopredictive capability for compounds whose solubility is sensitive to dynamic luminal conditions such as pH fluctuations, bile micelle formation and concentration, and the generation of digestion products during GI transit. Three complementary integration strategies were outlined: biopredictive dissolution input, mechanistic model parameterization, and evidence-based biopharmaceutics risk assessment. Firstly, a biopredictive dissolution case study combining TIM-1, TIM-2, and GastroPlus for a modified-release formulation of a BCS II compound showed how intrinsic dissolution variability under the fixed physiological conditions of TIM could support interpretation of clinical pharmacokinetic (PK) variability. Secondly, a case study demonstrated that while tiny-TIM correctly predicted food effects for 20/22 compounds across all BCS classes, the two incorrect predictions for atenolol and metformin were resolved by combining TIM data with GastroPlus to mechanistically model membrane transporters and permeability (*9*). Finally, when applied as a novel biopharmaceutics bridging risk assessment (BBRA) tool, a combined TIM-PBBM approach has been projected to reduce in vivo bridging studies by 70% (*10*). This highlights the potential power of integrating advanced in vitro and in silico tools as a comprehensive biopharmaceutics toolbox.

Dr. Rob Tzuchi discussed an internally developed biopredictive two-stage dissolution methodology for evaluating amorphous solid dispersion (ASD) performance without surfactants, where amorphous solubility and formulation robustness govern in vitro release. High rotational speeds (125 rpm) and mechanical shear via fluted disks were critical for success, particularly for erosion-based formulations, while an optimal filter size of 70 µm yielded the strongest in vitro–in vivo correlation, challenging the liquid-liquid phase separation (LLPS) nanoparticle assumption. The method demonstrated robust correlation with in vivo performance across multiple ASD platforms and conventional crystalline formulations, with sensitivity to batch-to-batch and supplier variability. Concurrent release of drug and functional excipients emerged as a potential surrogate marker for favorable bioavailability, while micro-CT imaging during dissolution provided complementary mechanistic insights into gel layer formation. Together, these analytical approaches were operationalized into a risk assessment matrix assigning risk levels to critical material attributes (CMAs), formulation variables (CFVs), and process parameters (CPPs) to guide method development and formulation design at AbbVie.

Prof. Aleksander Mendyk presented the application of artificial intelligence to optimize the development of orodispersible tablets (ODTs), which are valued for their near-instantaneous oral disintegration. He highlighted AI's unique capability to integrate multidimensional knowledge sources while remaining accessible through high-availability AutoML tools that no longer require specialized modeling expertise, a critical advantage given the vast landscape of excipients, manufacturing technologies, and equipment involved in ODT development. A case study demonstrated the use of automated machine learning (AutoML) to build predictive models for ODT disintegration time, emphasizing data quality as a prerequisite for model success. SHAP analysis of the best-performing model enabled meaningful knowledge extraction, providing qualitative validation aligned with domain expert understanding and demonstrating AI's potential to generalize knowledge and serve as a development guide. Prof. Mendyk concluded by integrating the ODT disintegration model into a larger modeling framework aimed at predicting drug release from modified-release ODTs, underscoring the broader impact of AI-driven decision support systems in streamlining formulation development and process optimization. Prof. Mendyk acknowledged his co-workers and both IVRDT and OBAM communities for the smooth and fruitful collaboration.

Dr. Mudie discussed two mechanistic case studies demonstrating how PBBM can elucidate food effects and guide dissolution specifications, reducing reliance on clinical studies. In the first case study, PBBM was applied to selumetinib, a weakly basic salt formulated as an immediate-release capsule and enteric-coated granules, revealing that the capsule's negative food effect stemmed from reduced dissolution and increased precipitation

in the higher-pH fed stomach, while enteric-coated granules were protected by delayed release after gastric emptying (*11*). Critically, the validated model defined a dissolution "safe space," demonstrating that slower dissolution in a virtual batch would not negatively impact clinical performance, providing a science-based regulatory basis for dissolution specifications. In the second case study, PBBM explained the atypical food effect of omaveloxolone, a highly lipophilic amorphous formulation showing an approximate 350% increase in C_{max} but only 15% increase in AUC following a high-fat meal, a phenomenon driven by enhanced bile salt solubilization increasing absorption in the upper small intestine where first-pass metabolism is highest, causing a transient Cmax surge without a proportional AUC increase (*12*). In both cases, PBBM provided mechanistic insights that in vitro data alone could not capture, demonstrating its power as a tool for informed formulation design, food effect interpretation, and robust regulatory decision-making.

Dr. David Turner (on behalf of Dr Divyen Shah) demonstrated the development and validation of physiologically based pharmacokinetic (PBPK) models for mesalamine, a locally acting treatment for mild-to-moderate ulcerative colitis, using the Simcyp population-based PBPK simulator (V24). Given mesalamine's low systemic bioavailability (15–30%) and high population variability, model development began with an intravenous bolus model to establish systemic disposition, incorporating extensive N-acetylation. The model was subsequently extended to oral dosing with mechanistic determinants including colonic degradation, pH-dependent solubility, regional intestinal permeability via the MechPeff model, and a segregated transit time model for GI transit dynamics (*13*). Three marketed formulations (Pentasa, Apriso, and Lialda) were incorporated using dissolution data generated at the University of Florida as direct inputs, with pH-triggered release functions applied for enteric-coated formulations. Simulated plasma concentration-time profiles showed good agreement with clinical data across intravenous and oral dosing studies, and predicted luminal and colon enterocyte concentrations were broadly consistent with available literature values (*14*). The work highlights that plasma PK alone is insufficient to reflect therapeutic performance for locally acting drugs, and it demonstrates the model's suitability for virtual bioequivalence analysis and safe space assessments for locally acting drug products. This work was supported by FDA Grant U01FD007662 in collaboration with the University of Florida.

KEYNOTE SESSION

Recent advances in biopharmaceutics have substantially reduced reliance on animal studies through improved in vitro methods, deeper mechanistic understanding of formulation performance, sophisticated in silico modeling, and more efficient human study designs. Despite this progress, animal models continue to provide value when they are mechanistically relevant, when in vitro–in vivo translation is not established, or when integrated into model-informed development strategies. This keynote presentation by Dr. Sperry reviewed five case studies highlighting both the strengths and limitations of animal studies. In one example, distal intestinal delivery of an oral peptide with a permeation enhancer showed markedly higher bioavailability in dogs compared with proximal delivery, but the translation to humans is questionable. Other cases demonstrated limited predictive value of dog studies for certain formulations, though PBBM often provided useful directional insight. In contrast, successful integration of in vitro dissolution with PBBM accurately predicted food and proton-pump inhibitor effects for a poorly soluble BCS Class II compound. In situations where in vitro and in silico tools yielded ambiguous results, targeted rat and dog studies helped resolve solid form selection challenges. Species-dependent translation remains a key limitation. While dog models are well established, pig and minipig models show promise due to physiological similarities to humans, with published examples demonstrating strong concordance in drug exposure and tolerability (*14, 15*). Advanced in vitro systems and predictive in silico approaches are increasingly central to formulation development, provided model uncertainty is explicitly considered. Innovative, integrated CMC–clinical studies further enable real-time formulation optimization using human pharmacokinetic data (*16*). Overall, the optimal development strategy combines mechanistic insight, advanced in vitro and in silico tools, and judicious use of animal studies to support efficient pharmaceutical development.

CONCLUSION

Taken together, presenters across industry and academia suggest practical takeaways for future scientists developing pharmaceutical drug products. First, they underscore the value of mechanistic thinking in understanding how formulation properties, GI physiology (including enzymes and food effects), and dosage-form design interact to influence bioperformance, rather than relying solely on empirical dissolution tests. Second, they show that combining advanced in vitro systems with in

silico tools can meaningfully improve absorption and exposure predictions, support better decision-making, and reduce late-stage risk. Third, the talks highlight how computational dissolution analysis can be tailored to specific technologies (e.g., ASDs, orodispersible tablets) to guide formulation optimization and clinically relevant specifications. Finally, speakers emphasize that animal models remain valuable when mechanistically relevant, when in vitro translation is uncertain, or when integrated into model-based development. Overall, these presentations underscored the importance of integrating biorelevant experiments, preclinical and clinical studies, and modeling and simulation early and iteratively to streamline and de-risk drug development.

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